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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/016,767	10/30/2001	Edward M. Atkinson	226272003310	3324

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EXAMINER	
HILL, MYRON G	
ART UNIT	PAPER NUMBER
1648	4

DATE MAILED: 04/23/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/016,767	Applicant(s) ATKINSON ET AL.	
	Examiner Myron G. Hill	Art Unit 1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8- 34 50, 51, 53- 92 118, 119, and 159- 16,* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8- 34 50, 51, 53- 92 118, 119, and 159- 16,* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

This office action is on claims 8- 34, 50, 51, 53- 92 118, 119, and 159- 162 drawn to a method of purification of rAAV using chromatography. Claims 1- 7, 35- 49, 52, 93- 117, 120- 158, and 163- 177 were canceled.

Objections to Claims

Claims 118 and 159 are objected to as being dependent upon a canceled claim, and must be rewritten to be independent or depend from a pending claim. These claims will be treated on their merits as they read on the current invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 50, 51, 53-92 as well as the claims that depend from them are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is not clear what the difference between rAAV pro-vector (defined page 19 line 8) and rAAV vector (page 21 lines 14- 30) is or if terms are identical. In claim 60 the meaning of "split-packaging gene" is not clear. In claim 82 the terms "HS resin" is taken to mean heparin sulfate and "SP resin" is not defined in the claim or specification.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 8- 34, 118, 119, and 159- 162 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tamayose et al. (Human Gene Therapy 1996, 7: 507- 513), further in view of Fanget et al. (2/20/1997 WO 97/06342, from IDS), and O'Riordan (6/3/1997, WO 97/08298, from IDS).

These claims are drawn to a method of purifying rAAV particles from cell lysate or supernatant by steps including anion and cation chromatography and filtration.

Tamayose teaches that rAAV can be purified from lysed cells as well as supernatant, or from both, growing cells with less culture medium and freeze-thawing to lyse cells (page 510, column 1, first full paragraph). Sulfonated cellulose chromatography was used to concentrate the virus containing solutions (page 510, middle). This step was indicated to have nearly 100% recovery of virus and a 50 fold increase in titer without a loss of biological activity. Tamayose also teaches that this technique alone is not sufficient for purification (page 512, column 2, lines 16-17).

Fanget broadly teaches the use of cation and anion chromatography columns in combination to purify virus for vaccine use (abstract). Resins include EMD TMAE (an N-charged amino resin), DEAE (an anion exchange resin).

O'Riordan discloses a method of purification of rAAV substantially as claimed. O'Riordan discloses methods for purifying rAAV with the stated result "to rapidly and efficiently purify commercial level quantities of active (infectious) virus suitable for use in therapeutic applications, e.g. gene transfer/ therapy procedures."(page 1, lines 14-17) For purification of rAAV, O'Riordan uses filtration to clarify lysates and ion-exchange and other types of columns to purify and concentrate the particles (pages 17- 21) as well as virus specific ligands (antibodies) (page 6, lines 13- 16). O'Riordan also states that other columns can be used to purify AAV and discloses the use of heparin (page 6, line 14) and cation columns (page 15, lines 24- 34) to purify adenovirus.

Knowing the rAAV of Tamayose required more purification, one of skill in the art would look for additional methods to add to the steps in the purification procedure. Both O'Riordan and Fanget provide additional mediums to purify the rAAV (anion and cation resins include- N-charged amino, TMAE resin, sulfo- resin, heparin sulfate (HS resin), and DEAE resin). It would have been routine experimentation to use a variety of different chromatographic materials to determine which ones and which combinations give the highest purity, highest percent recovery, and highest titer of infectious rAAV. One of skill in the art would also know to use the methods to grow greater amounts of virus as well as additional techniques to handle larger sample volumes (filtration). Also, one skilled in the art would know the importance of clarifying the lysate prior to chromatography as taught by O'Riordan.

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art to obtain high titer, pure stocks of rAAV with a reasonable expectation of success.

Claims 50, 51, 53- 92 rejected under 35 U.S.C. 103(a) as being unpatentable over Tamayose et al. (Human Gene Therapy 1996, 7: 507- 513), Fanget et al. (2/20/1997 WO 97/06342, from IDS), and O'Riordan (6/3/1997, WO 97/08298, from IDS), as applied to claims 8- 34, 118, 119, and 159- 162 above, and further in view of Shenk (US Pat 5,~~346~~436,146).

These claims are drawn to a method of producing rAAV particles and purifying them by chromatography.

Shenk discloses a method of producing a rAAV by cotranfecting producer cells having a heterologous DNA flanked by at least one inverted terminal repeat (ITR), helper AAV DNA coding one or more AAV packaging proteins needed for replication and encapsidation, and helper virus, in this case adenovirus (Column 12, lines 49- column 13, line 12). Shenk also teaches that AAV helper genes can be linked to a variety of promoters/and regulatory sequences including inducible promoters (columns 11-12), packaging genes can be stably integrated into the producer cell (column 12, lines 6- 38) and introduction of rAAV vector can be done prior to infection, simultaneously to infection, or after infection (column 12, lines 60- 64).

Shenk does not teach all the specifics about culture conditions or purification.

Tamayose, Fanget , and O'Riordan teach methods of purification as discussed above. O'Riordan additionally teaches the use of microfluidization (page 36, line 18) and Benzonase (page 17, line 33). The length of time infected cells are incubated before harvest would be a variable determined by normal optimization for best yield.

Thus, one of ordinary skill in the art would have been motivated to use additional steps of purification when using the method of Tamayose to purify the virus of Shenk.

It would have been prima facie obvious to grow rAAV under conditions for optimal yield and purify to achieve high titer, pure stocks.

Claims 62- 64 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tamayose, Fanget, O'Riordan, and Shenk as applied to claims 50, 51, 53- 92 above, and further in view of Myers et al. (Journal of Virology 1980 35: 65- 75).

Shenk, Tamayose, Fanget , and O'Riordan as discussed above, teach a method to produce rAAV and purification methods.

Shenk, Tamayose, Fanget , and O'Riordan do not teach using a ts virus.

Myers teaches that Ad5ts149 was an efficient helper of AAV in contrast to other ts viruses examined (abstract). Meyers teaches that the ts viruses at non-permissive temperatures grow to 5 logs less titer (page 66, column 1, end of second full paragraph).

The properties of ts adenovirus were well known in the art and it would be obvious to one skilled in the art to increase the purity of the rAAV of Shenk by reducing the amount of contaminating helper-virus.

Thus, it would have been prima facie obvious to use Ad5ts149 virus to produce rAAV that is more pure.

Claim 34 rejected under 35 U.S.C. 103(a) as being unpatentable over Tamayose et al. (Human Gene Therapy 1996, 7: 507- 513), Fanget et al. (2/20/1997 WO 97/06342, from IDS), and O'Riordan (6/3/1997, WO 97/08298, from IDS) as applied to claims 8- 34, 118, 119, and 159- 162 above, and further in view of Graham (*J. Gen. Virol.*1987, vol. 68 pages 937- 940).

Tamayose, Fanget, and O'Riordan teach methods of purification of virus as taught above.

Tamayose, Fanget, and O'Riordan do not teach using suspension cultures for producing rAAV particles.

Graham teaches adapting cells to grow in suspension and that cells grown in suspension offer advantages over cells grown in monolayers in terms of efficiency, economy and potential automation of large scale production (page 939, last paragraph).

Thus, it would have been obvious for one skilled in the art to use suspension cultures to produce large quantities of rAAV using the method of Graham.

It would have been *prima facie* obvious to use suspension cultures to produce large quantities of rAAV.

Claims 87, 88, and 92 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tamayose, Fanget, O'Riordan, and Shenk as applied to claims 50, 51, 53- 92 above, and further in view of Graham.

Tamayose, Fanget, and O'Riordan teach methods of purification of virus as taught above. Shenk teaches a method to make rAAV.

Shenk, Tamayose, Fanget, and O'Riordan do not teach using suspension cultures for producing rAAV particles.

Graham teaches that cells grown in suspension offer advantages over cells grown in monolayers in terms of efficiency, economy and potential automation of large scale production (page 939, last paragraph).

Thus, it would have been obvious for one skilled in the art to use suspension cultures to produce large quantities of rAAV of Shenk using the culture method of Graham.

It would have been *prima facie* obvious to use suspension cultures to produce large quantities of rAAV.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Myron G. Hill whose telephone number is 703-308-4521. The examiner can normally be reached on 9am-6pm Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 703-308-4247. The fax phone number for the organization where this application or proceeding is assigned are 703-308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Myron G. Hill
Patent Examiner
April 19, 2002

MARY E. MOSHER
PRIMARY EXAMINER
GROUP ~~1800~~ 1600